SYNOPSIS

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL FUSED PYRIMIDINE AND OXAZINE HETEROCYCLES

SHORT RESUME OF THE PLAN PROPOSED FOR INVESTIGATION FOR Ph.D. DEGREE UNDER THE FACULTY OF SCIENCE

To be submitted to

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED

By

Mr. P. S. KALE

(Research Scholar)

Assistant Professor

Shri Tejmal Gandhi Junior Science College,

Brahmangaon.

Under the Guidance of

Dr .S.B.SIRSAT

(Research Guide)

Assistant Professor

Department of Chemistry,

Yeshwant College, Nanded.

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Thesis Title

Synthesis, Characterization and Biological Evaluation of some Novel Fused pyrimidine and Oxazine Heterocycles.

Introduction:-

Fused pyrimidine and Oxazine with its derivatives are important nitrogen and oxygen containing heterocyclic compounds of various biologically interesting properties with several pharmaceutical applications. Substituted pyrimidine and Oxazine are an important classes of benzohetrocycles which constitutes the building blocks of wide range of pharmacologically active compounds having antibacterial, antifungal, anticancer, antitubercular, antileishmanial, and antimalarial and antidepressant activities. Also, pyrimidine and Oxazine have been reported to show antimicrobial, novel potent antithrombotic, anti-pain and anti-inflammatory activities.

In recent years, the synthesis of fused bicyclic heterocyclic compounds possessing an pyrimido- Oxazine & Pyrimido pyrimidine central core has been the focus of great interest. This type of compounds shows various biological properties such as antibacterial, antiallergic, anti-inflammatory, antitumor, phsphodiesterase inhibition and ant Parkinsonism, many workers have synthesized different 1, 3-oxazine. Oxazine are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities.

In recently substituted Oxazine are prepared using different chalcones and that are very versatile substrates for the evolution of various reactions and physiologically active compounds. The reaction of thiourea with chalcone (Michael acceptor) results in 1, 3 Oxazine and reaction of chalcone with guanidine results in 1, 3-pyrimidines. It has been well focused that the presence of pyramid-Oxazine and pyrimido pyrimidine with various chemically reactive moieties is an important structural feature and also substituted imino and Oxo group present in Oxazine and pyrimidine ring, and the resulting molecule would exhibit promising biological activities. In continuation of our work. In this work our paln to synthesize , pyrimido- Oxazine and pyrimido pyrimidine containing more reactive functional groups for further cyclisation and derivatization . The synthesized compounds reacting with various nucleophiles such as substituted aromatic amines, aromatic phenol, various active methylene compound and alicyclic heterocyclic compound construct pyrimido pyrimidine and pyrimido Oxazine derivatives.

LITERATURE SURVEY:-

- El-Hossini M.S. *et.al*. Reported the reaction of ethyl cyanoacetate with α-cyano chalcone, which lead to the formation of a β- enaminoester via Michael addition. This was reacted with ethyl cyanoacetate, phenyl isothiocyanate and trichloroacetonitrile to yield the pyranopyrimidine compounds which showed antibacterial activities.
- Olaf D.K. *et.al.* Described an efficient and reliable synthesis of the heterocyclic scaffold 3-hydroxy-4oxo-4H-pyriod [1, 2-a] pyrimidine -2- carboxylate, which allows the substituents on pyrimido fused ring. Thus they devised a new scaffold for HIV-1 integrase inhibitors.
- Sekhar N.M., *et.al.* Developed a short and efficient synthesis for pyrazolo [2, 3-d] pyrimidine by cyclo condensation of α, α -dibromo aldehydes with 2, 4 –diamino-6-hydroxy pyrimidine under mild basic conditions in good yields. Application of this protocol has been demonstrated in the synthesis of a metabolite of pemetrexed disodium, a novel multi targeted antifolate.
- Glotova *et.al.* synthesize 1-Acyl-2-bromoacetylene derivatives when treated with Thiourea in the presence of glacial acetic acid produce α-Oxo ketene mercaptals. The Latter in $BF_3.Et_2O$, with the removal of cyanamide and water undergoes Intermolecular cyclization to give 1, 3- Oxazine-6-thione hydro bromide which on Recrystallization with water-alcohol yields pure substituted 2-amino-1, 3-thiazine-6-Thiones

- **Objectives :**

- Specific objectives of our current research program include the synthesis of novel Pyrimido pyrimidine and pyrimido Oxazine and their derivatives.
- One pot synthesis of amino pyrimidine and amino Oxazine**.**
- Reaction of amino pyrimidine and amino Oxazine nucleus with Michael acceptor to give pyrimido pyrimidine and pyrimido Oxazine.
- Reaction of pyrimido pyrimidine and pyrimido Oxazine nucleus with various aromatic phenols.

- Reaction of pyrimido pyrimidine and pyrimido Oxazine nucleus with various aromatic amines.
- Reaction of pyrimido pyrimidine and pyrimido Oxazine nucleus with various Hetryl amines.
- Reaction of pyrimido pyrimidine and pyrimido Oxazine nucleus with various Benzothiazole.
- Biological activity of above synthesized compounds.

- **Methodology :**

- By known three component system synthesis of amino pyrimidine and amino Oxazine.
- The synthesized amino pyrimidine and amino Oxazine is act as a Michael donor and it nucleophilically condense with Michael acceptor to give pyrimido pyrimidine and pyrimido Oxazine.
- Pyrimido pyrimidine and pyrimido Oxazine act as electrophilic species condense with various nucleophile such as aromatic amines, aromatic phenols, heteryl amines etc.
- Biological evaluation of above synthesized compounds.

- **International status :**

Since from the last three decades, we have witnessed the revolutionary synthesis Pyrimido pyrimidine and pyrimido Oxazine of many researchers throughout the world. Although there are huge number of articles on pyrimido pyrimidine and pyrimido Oxazine.

1. Pecorari P, Rinaldi M, etal Synthesis and biological activity of pyrimido [2,1-b] [1,3]thiazine, [1,3]thiazino[3,2-a]purine and [1,2,3]triazolo[4,5-d] [1,3]thiazino[3,2-a] pyrimidine derivatives and thiazole analogues.

2. Covington R.R; Temple D.L., YevichJ.P. (1982) “Antial- lergics: 3-(1H- tetrazol-5-yl) - 4H-pyrimido [2, 1- b] ben-zothi- azol-4-ones,” Journal of Medicinal Chemistry, Vol. 25, No. 7, pp. 864-868.

3. Wade JJ, Toso CB, Matson CJ, Stelzer VL (1983) Synthesis and antiallergic activity of some acidic derivatives of 4H-pyrimido[2,1- b] benzazol-4-ones. J Med Chem 26: 608-611

- **National Status :**

Apart from the international contribution some of the Indian researchers have also Made their mark on synthesis of pyrimido pyrimidine and pyrimido Oxazine. In this Section some of the research groups can be mentioned like

1. V. Sundari G. Nagarajan S. Gurumurthy and R. Valliappan (2009), synthesis characterization and biological activities of 3, 5-Diaryltetrahydro-N-[(phenyl amino) methyl]-1, 4-thiazine-1, 1-dioxide.
2. Vachala S. Dinakaran, Bhargavi Bomma and keloth K. srinivasan (2012) synthesized fused pyrimidine the heterocycles of diverse biological and pharmacological significance.

- **Regional status :**

1. Sambhaji P. vartale, Vijay N.Bhosale, Sandeep V. Khansole and ramdas N. Katapalle (2009). A convenient one pot synthesis of 3-cyno-9-methyl-2-methylthio-4-oxo-4H-pyrimidi-[2, 1-b] [4, 5-b] quinoline and its reaction with selected nucleophiles. Letters in organic chemistry Vol.6, No7, 544-548.
2. Baheti KG and Kuberkar SV "Synthesis and biological activity of 4H- pyrimido [2, 1-b] benzothiazole-8-substituted-2-thiomethyl-3-cyano-4-ones." (2003) Ind J Het Chem 12: 343D.
3. Baheti KG, Jadhav JS, Suryawanshi AT and Kuberkar SV (2005) Novel synthesis and antibacterial activity of 15-iminobenzothiazole [2,3b] pyrimido [5,6e] pyrimido [2,3] benzothiazole-14-H ones and its 3,10 substituted derivatives. Ind J Chem 44B: 834D

4. Pingle MS, Vartale SP, Bhosale VN and Kuberkar SV (2006) A convenient synthesis of 3-cyano-4-imino-2- methylthio-*4H*pyrimido [2, 1-*b*] [1, 3] benzothiazole and its reactions with selected nucleophiles Arkivoc X, 190D.
5. Vartale SP, Jadhav JS, Kale MA and Kuberkar SV (2006) Synthesis and antimicrobial activity of 6/7/8- substituted-1-[aryl/6'-substituted-2'-benzothiazolyl]-pyrazolo [4, 5-b] quinolines Ind J Chem.

- **Scope of the study :**

A lot of research work is going on all over the world to investigate organic compounds which will act as effective medicines as anti-HIV, anti-Cancer and anti - tuberculostatic drug Antibacterial. National Institutes of Health, National Cancer Institute, Bethesda, Maryland, USA showed keen interest in evaluation of compounds, identified in our earlier research publications for andti - HIV and anti-cancer screening. It is surmised that some newly synthesized compounds mentioned in our proposal would exhibit properties required for effective drugs. Synthesis and screening of newly synthesized compounds would lead to the formation of pharmacological important compounds as a good antibacterial.

Proposed work plan with tentative chapter scheme.

Year	Quarters (Periods of three months)	Milestones
Year I	1 st Quarter	Reference Work
	2 nd Quarter	Topic first literature survey
	3rd Quarter	Topic second Experimental Work and characterization
	4th Quarter	Topic second Experimental Work and characterization
Year II	1 st Quarter	Topic third Experimental Work and characterization
	2 nd Quarter	Topic third Experimental Work and characterization
	3rd Quarter	Topic Fourth Experimental Work and characterization
	4th Quarter	Topic Fourth Experimental Work and characterization
Year III	1 st Quarter	Topic Fifth Experimental Work and characterization
	2 nd Quarter	Topic sixth Biological evaluation
	3rd Quarter	Topic sixth Biological evaluation
	4th Quarter	Writing and typing of the research work and submission of the research work

- **Expected Outcome :-**

It is planned to synthesize newly designed compounds which are free from toxic effects and possess good biological activity.

- **References :-**

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Mr. P. S. Kale
(Research Scholar)
Jr. Lecturer
Shri. Tejmal Gandhi Junior Science College, Brahmangaon

Dr. S. B. Sirsat
(Research Guide)
Assistant Professor
P.G. Department of Chemistry
Yeshwant College, Nanded

Dr. S. B. SIRSAT
M.Sc. SET, Ph.D
Assistant Professor
Department of Chemistry
Yeshwant Mahavidyalaya, Nanded

Cell No. 9890374904
Off (Ph) 02462 – 254170, 269616
Email : sbs.igm@gmail.com

To,

The Registrar,

S.R.T.M. University, Nanded.

Subject : **Submission of synopsis of the research topic entitled "Synthesis, Characterization and Biological Evaluation of some Novel Fused pyrimidine and Oxazine Heterocycles".**

Respected Sir,

With Reference to the subject cited above, I have to state that Mr. Prashant Sambharao Kale. Research scholar registered for Ph. D. under my guidance by research allocation committee, I wish to submit plan of his proposed research work as a synopsis.

You are Kindly requested to accept it and do the needful.

Thanking You Sir !

Your faithfully

Dr. S. B. SIRSAT

Enclose –

1. Certificate of R.A.C.
2. M.Phil. Exempted certificate
3. Synopsis